



# FREEDOM-DM1: A Phase 1, Placebo-Controlled Single Ascending Dose Study To Evaluate PGN-EDODM1 in People With Myotonic Dystrophy Type 1 (DM1)

Jane Larkindale, DPhil, VP Clinical Science, PepGen

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Authors: Jennifer Shoskes<sup>1</sup>, Johanna Hamel<sup>2</sup>, Jean Dennis Brisson<sup>3</sup>, Hanns Lochmuller<sup>4</sup>, Thurman Wheeler<sup>5</sup>, Jacinda Sampson<sup>6</sup>, Namita Goyal<sup>7</sup>, Jane Larkindale<sup>1</sup>, Brijesh Garg<sup>1</sup>, Gregory Song<sup>1</sup>, Pallavi Lonkar<sup>1</sup>, Stephen Babcock<sup>1</sup>, Shaoxia Yu<sup>1</sup>, Patricia Fraser<sup>1</sup>, Michelle Mellion<sup>1</sup>

Affiliations: 1. PepGen Inc. 2. University of Rochester, Rochester, NY 3. CIUSSS du Saguenay-Lac-Saint-Jean, Canada 4. The Ottawa Hospital, Canada. 5. Massachusetts General Hospital, Boston MA 6. Stanford University Medical Center, Stanford CA 7. University of California - Irvine Medical Center, Irvine CA

## Disclosures

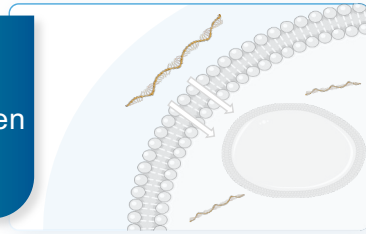
- Jane Larkindale is a full-time employee of PepGen Inc
- Jane Larkindale receives compensation, equity and benefits from PepGen Inc
- The study and current analysis were sponsored by PepGen Inc



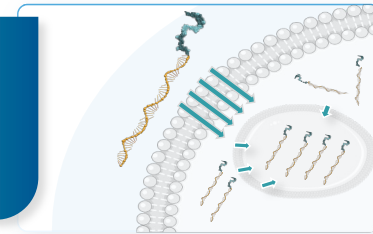
Driven by our proprietary Enhanced Delivery Oligonucleotide (EDO) platform, PepGen is creating a pipeline of disease-modifying therapeutics with the potential to safely and effectively target the underlying cause of serious genetic neuromuscular and neurological diseases

# Enhanced Delivery Oligonucleotide Platform Enhances Nuclear Delivery and Uptake of Oligonucleotides

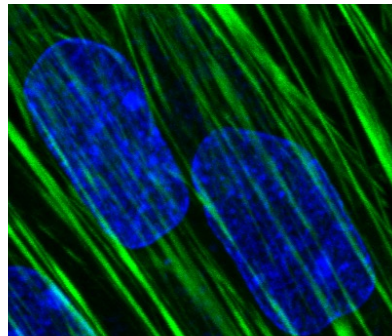
Naked oligonucleotides not efficiently taken up into muscle cells & nucleus



EDOs enhance nuclear delivery of oligonucleotide therapeutics

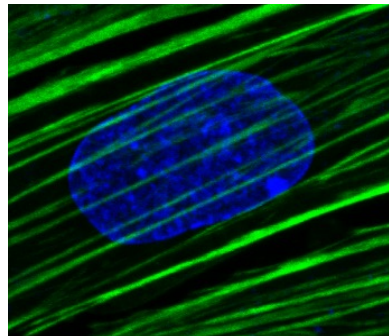


Not treated



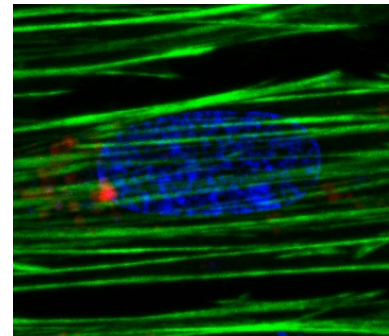
0  $\mu$ M

PGN-PMODM1

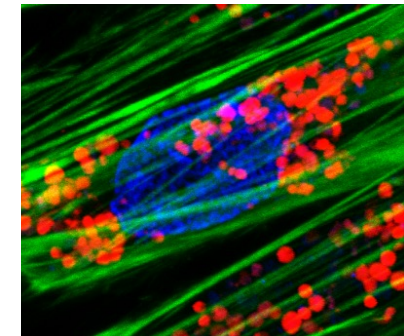


20  $\mu$ M

PGN-EDODM1



2  $\mu$ M

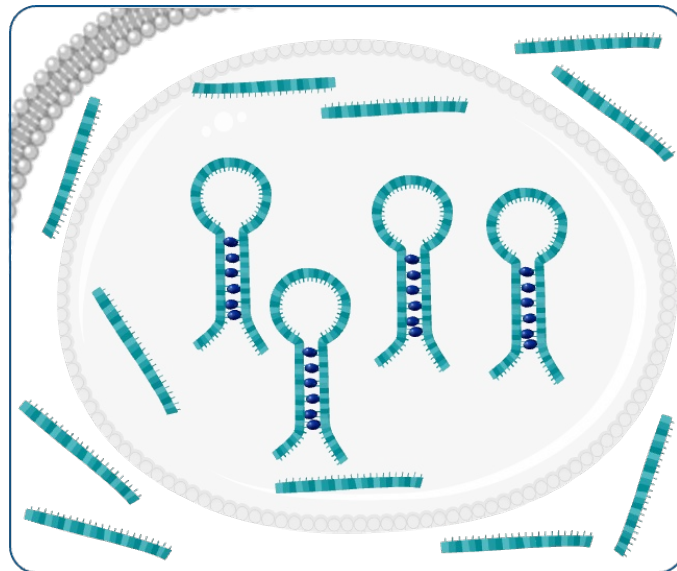


10  $\mu$ M

PGN-EDODM1 / Actin / Nucleus

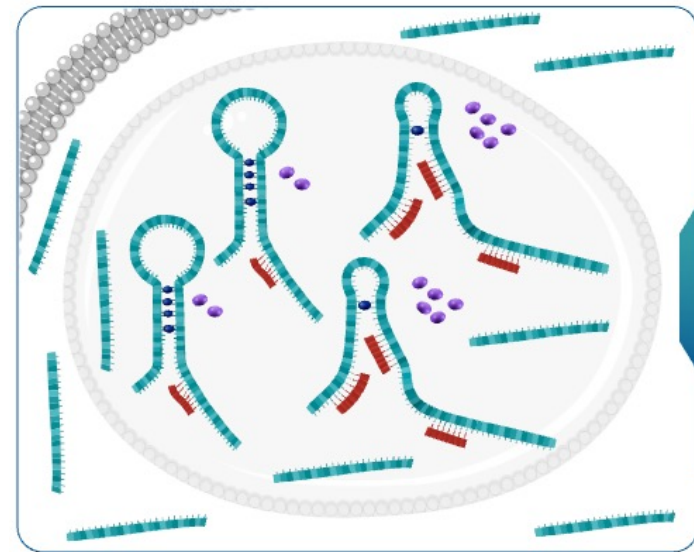


# DM1 is Caused by Pathogenic CUG Repeats in *DMPK* RNA that Sequester Splicing Factors. PGN-EDODM1 is Designed to Bind to the Repeat Sequence and Liberate MBNL1



Trapped  
MBNL1 is  
inactive and  
results in  
mis-splicing

- DM1 is caused by pathogenic *DMPK* transcripts containing CUG repeat sequences that form hairpin loops.
- These hairpin loops trap MBNL1 proteins that are needed for correct splicing of mRNAs.



Liberated  
MBNL1  
restores  
correct  
splicing

- PGN-EDODM1 binds selectively to the pathogenic *DMPK* transcript.
- This reduces the ability of the CUG repeats to form hairpin loops and sequester RNA splicing proteins.

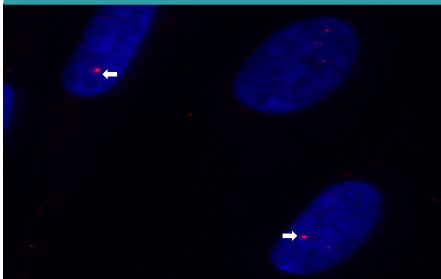
# PGN-EDODM1 Reduced Pathogenic Nuclear Foci, Liberated MBNL1 and Corrected Mis-Splicing in Patient Cells with Long CUG Repeats

## Foci Reduction

### Not Treated



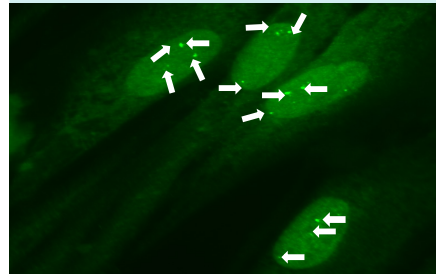
### PGN-EDODM1 Treated



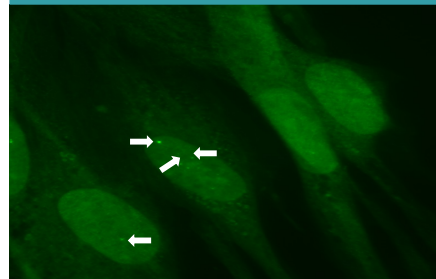
**54%**  
reduction in  
toxic foci

## MBNL1 Liberation

### Not Treated

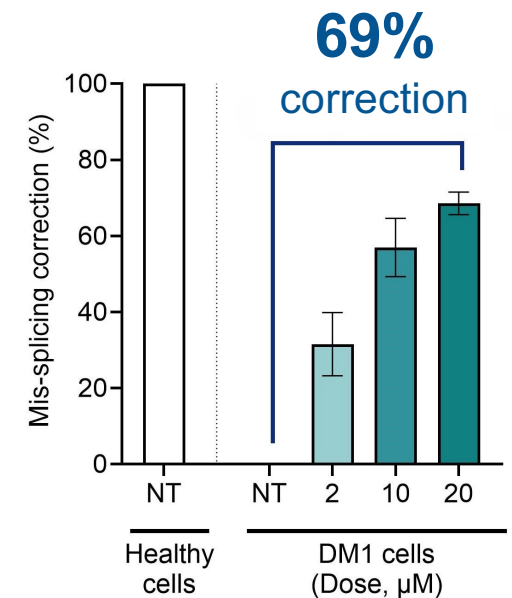


### PGN-EDODM1 Treated



## Mis-Splicing Correction

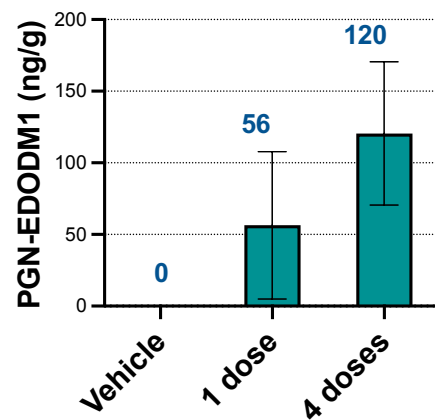
*Across multiple transcripts*



# Multiple Doses of PGN-EDODM1 Led to Greater Improvement in Splicing Correction and Myotonia vs Single Dose in Preclinical Studies

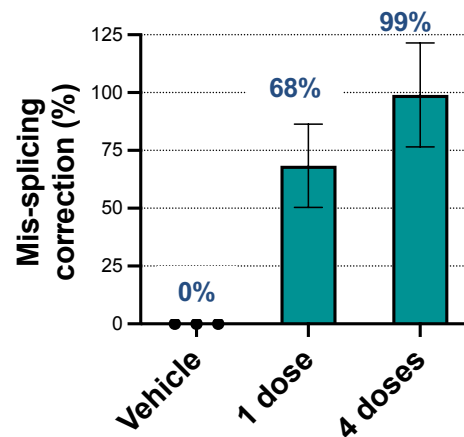
## Tissue Concentration

### Skeletal muscle



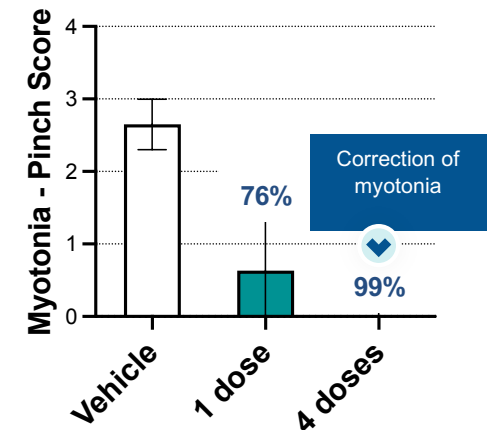
## Mis-splicing Correction

### Across multiple transcripts



## Correction of Myotonia

### Pinch test



# FREEDOM: Phase 1 PGN-EDODM1 Single-Ascending Dose Study Design



## FREEDOM Study Overview

Multinational, randomized, double-blind, placebo-controlled SAD study in people with DM1

Single IV administration of PGN-EDODM1

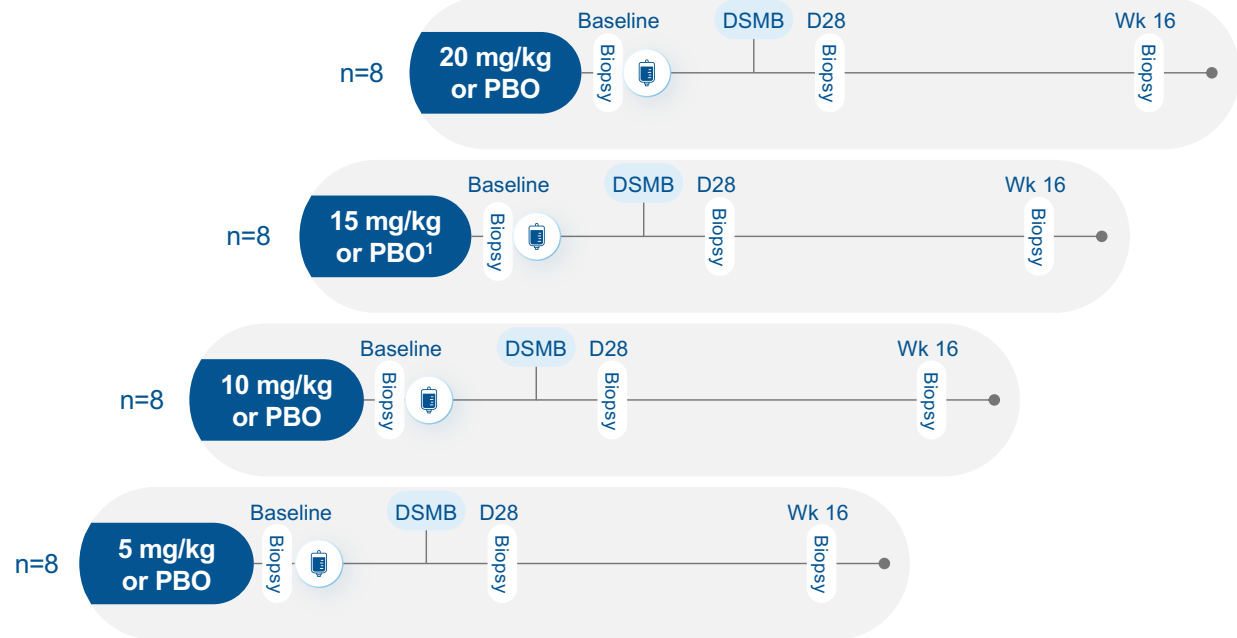
Muscle biopsies in tibialis anterior at Baseline, Day 28, Week 16

Safety, PK, correction of mis-splicing, initial functional assessments

## Single Dose PGN-EDODM1 or Placebo (randomized 3:1)

Dosing

Dosed



1.15 mg/kg cohort added to expand pharmacokinetic and pharmacodynamic understanding  
DSMB: data safety monitoring board; IV: intravenous; PBO: placebo; SAD: single-ascending dose; PK: pharmacokinetics



PGN-EDODM1 dose



## FREEDOM: Demographics and Baseline Characteristics in First Two Cohorts

	Mean (SD) or n (%)		
	Placebo (n=4)	5 mg/kg (n=6)	10 mg/kg (n=6)
Age (years)	39.0 (10.9)	36.3 (9.0)	34.7 (8.2)
Female, n (%)	3 (75%)	3 (50%)	3 (50%)
BMI (kg/m <sup>2</sup> )	20.0 (3.3)	22.8 (5.0)	22.8 (5.7)
Splicing Index	72.3 (16.3)	73.7 (15.2)	53.6* (26.0)
vHOT – middle finger (sec)	14.1 (5.6)	12.6 (7.3)	9.3 (2.8)
10MWRT (sec)	4.3 (1.6)	3.9 (1.5)	4.4 (1.5)



\*n=5 as one participant's sample showed splicing index outside the pre-specified assay range at Baseline (no detectable mis-splicing)  
 Splicing Index (SI) Mild = 0–0.4, SI Moderate = 0.41–0.75, and SI Severe = 0.76–1.0. Provenzano, et al.  
 SD: standard deviation; BMI: body mass index; PBO: placebo; vHOT: video hand opening time; 10MWRT: 10-meter walk run test

# Favorable Emerging Safety Profile of PGN-EDODM1<sup>1</sup>

## Summary of Treatment Emergent Adverse Events (TEAEs)

	5 mg/kg (n=8) <sup>2</sup> n(%)	10 mg/kg (n=8) <sup>2</sup> n(%)	Total (n=16) <sup>2</sup> n(%)
Any TEAE	4 (50.0)	6 (75.0)	10 (62.5)
Any related TEAE	1 (12.5)	3 (37.5)	4 (25.0)
Any SAE	1 (12.5)	2 (25.0)	3 (18.8)
Any related SAE	0	1 (12.5)	1 (6.3)
Any AESI or dose-limiting toxicities	0	0	0
Any TEAE leading to study withdrawal	0	0	0
Any TEAE leading to death	0	0	0

## PGN-EDODM1 was Generally Well-Tolerated, with Most TEAEs Mild or Moderate in Severity

### All treatment related TEAEs:

- Nausea (n=2), vomiting (n=1), dizziness (n=1), headache (n=1), feeling hot (n=1), abdominal pain (n=1)
- SAE related to study drug:
  - Abdominal pain (10 mg/kg) potentially confounded by use of prohibited, off-label drug taken on the morning of PGN-EDODM1 dosing<sup>3</sup>
- SAEs unrelated to study drug:
  - Appendicitis (5 mg/kg)
  - Right anterior tibial artery pseudoaneurysm (10 mg/kg) related to muscle biopsy procedure
- No adverse events related to electrolytes or renal biomarkers



1. As of December 3, 2024

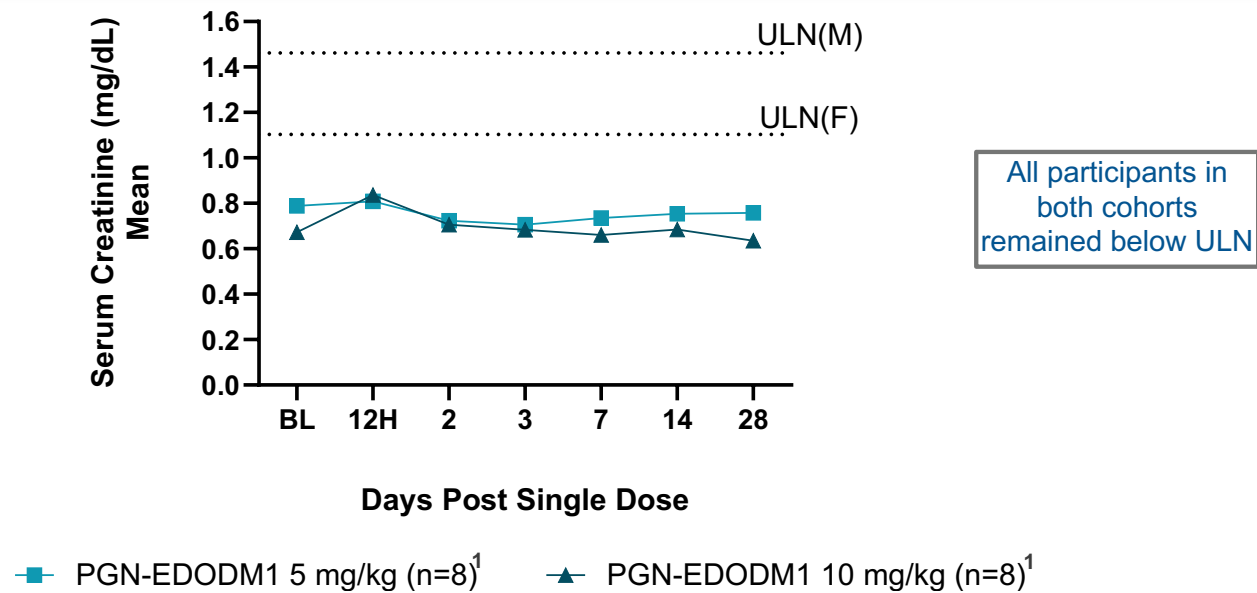
2. Includes all participants (placebo and PGN-EDODM1 treated); cohorts remain blinded

3. Data Safety Monitoring Board reviewed event and recommended continuation of study/dosing

SAE: serious adverse event; AESI: adverse event of special interest

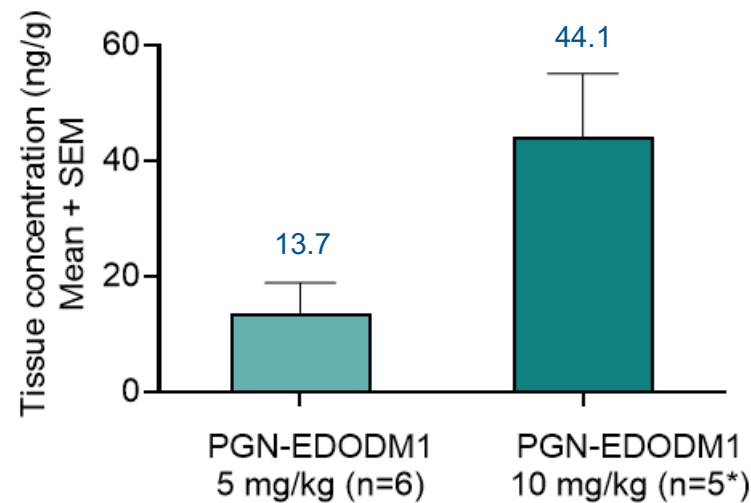
## PGN-EDODM1 Demonstrated Normal Mean Serum Creatinine Levels

### Serum Creatinine



# PGN-EDODM1 Observed to Have Robust and Dose-Dependent Increases in Muscle Tissue Concentration Following a Single Dose

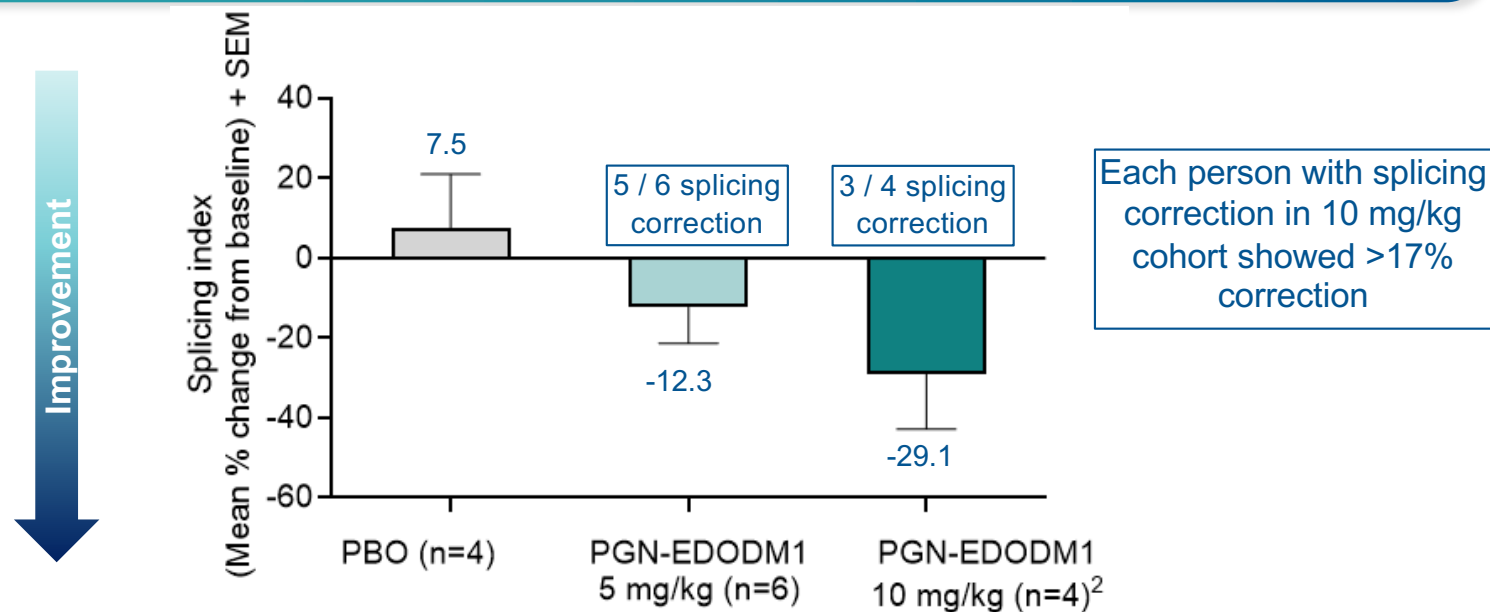
## Muscle Tissue Concentration at D28





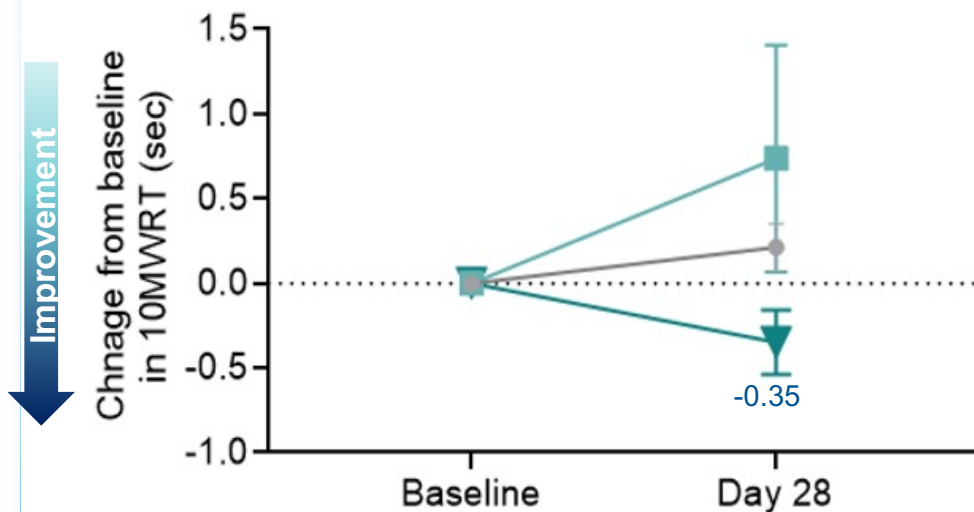
# PGN-EDODM1 Produced Mean 29% Splicing Correction Following Single 10 mg/kg Dose

Splicing Index Changes: 22-Gene Panel<sup>1</sup> at D28

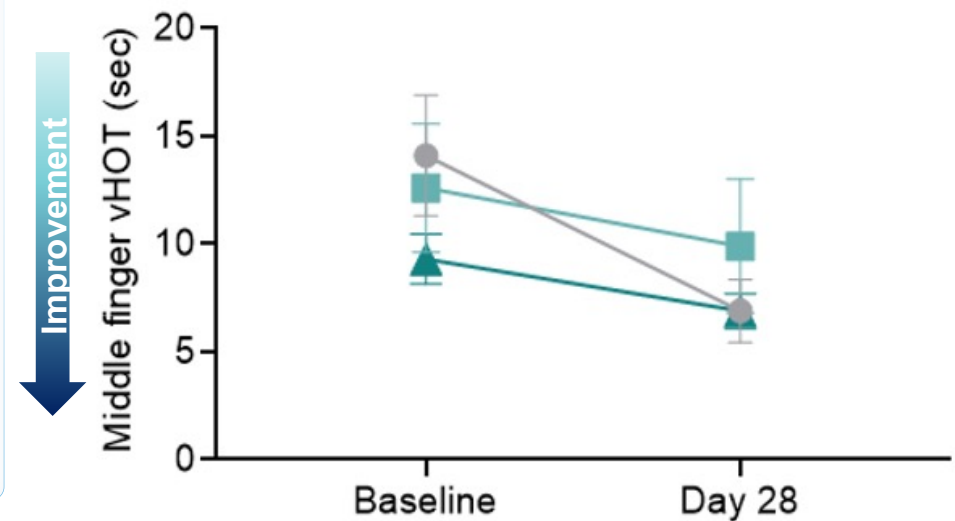


## Functional Outcomes Data After a Single Dose

10-Meter Walk Run Test (10MWRT) at D28



Myotonia (vHOT) at D28



● PBO (n=4) ■ PGN-EDODM1 5 mg/kg (n=6) ▲ PGN-EDODM1 10 mg/kg (n=6)

# PGN-EDODM1 Selectively Targets Only Pathogenic *DMPK* to Correct RNA Mis-Splicing



**Favorable emerging safety profile<sup>1</sup>** in people with myotonic dystrophy type 1



Dose-dependent increase in drug **tissue concentration** observed in first two cohorts



Dose-dependent increases in evaluable people<sup>2</sup> in mean **splicing correction** following single dose

**~29%** at 10 mg/kg

**~12%** at 5 mg/kg

# FREEDOM2 Phase 2 MAD Study Underway



## FREEDOM2 Study Overview

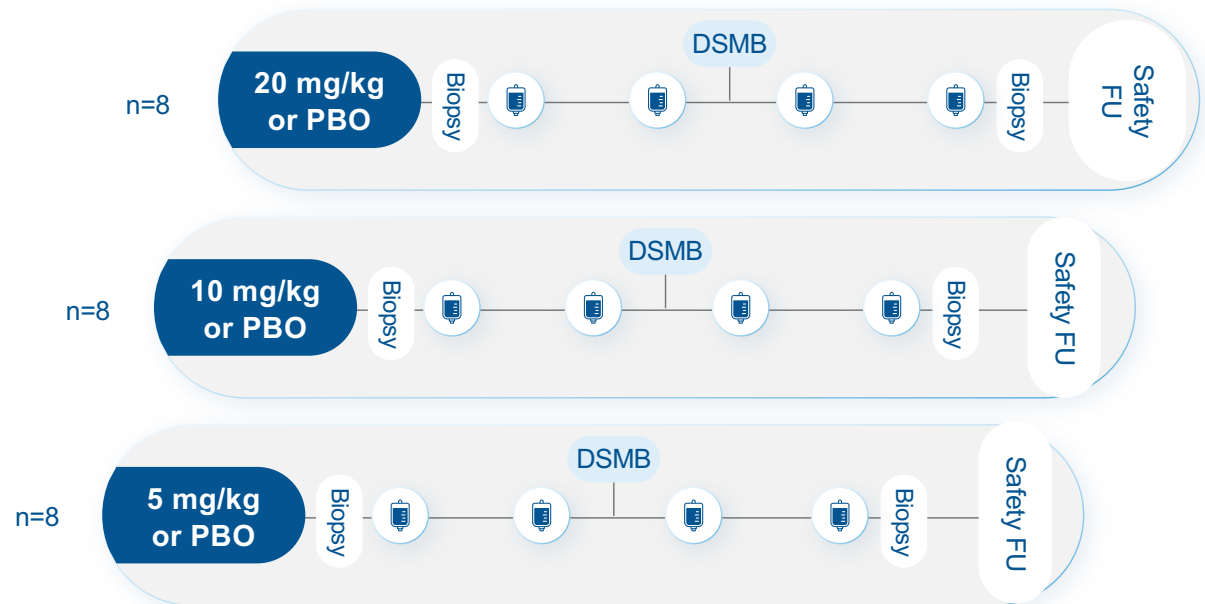
Multinational, randomized, double-blind, placebo-controlled, MAD study open in UK and Canada

IV administration of PGN-EDODM1 or placebo every 4 weeks for a period of 12 weeks

Key endpoints: Safety, PK, correction of splicing, functional assessments: vHOT, hand grip, 10-meter walk run test

### 4 Doses of PGN-EDODM1 or Placebo (randomized 3:1)

Dosing



DSMB: data safety monitoring board; FU: follow-up; IV: intravenous; MAD: multiple-ascending dose; PBO: placebo; PK: pharmacokinetics; vHOT: video hand opening test



PGN-EDODM1 dose every 4 weeks



# Thank you!



**Clinical study  
participants and  
their families**



**Clinical site staff  
and  
investigators**



**Community  
and clinical  
advisors**



**Preclinical  
collaborators**

See posters P48 and O45 for more information